# ENHANCEMENT OF DRUG DISTRIBUTION BY ION-PAIR FORMATION

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The formation of ion-pair species is used in the pharmaceutical sciences to enhance the transport of charged molecules into lipophilic phases,(drug absorption,analysis). As part of our continuing interest in such species (e.g. Tomlinson and Davis 1980), we have studied ion-pairing between a model solute, chloramphenicol succinate (CAS), and substituted phosphonium salts, and both the diffusion of such species through artificial membranes and their effect on CAS loss from a ocular perfusion device. Comparison has been made with the transport of chloramphenicol itself (CA) with cognizance of the facts that CAS can exist as an equilibrium mixture of 1- and 3-succinates, and can hydrolyse to CA, (Burke et al 1980). CAS forms ion pairs with positively charged ions at physiological pH, and phosphonium salts were chosen as model cationic organic ions having negligible surface activity. Enhanced partitioning into a lipid phase by ion-pair formation was examined using a two-phase titration system (pH 7.4) with continuous spectrophotometric monitoring (Cantwell and Mohammed 1979),(Table 1). Passage of CAS across an artificial membrane,(polyethylene impregnated with buffer saturated octan-1-ol) was followed using a rotating diffusion cell (Albery et al 1976).The data given as loss of CAS from the donor compartment, indicate that the transport of the ionised species can be enhanced greatly by the oppositely charged ion (Table 2), and that this can at least approach the loss for the uncharged CA species.

Table 1. Ion-pair extraction of CAS using tetraphenylphosphonium bromide (TPP)

| CAS($\times10^{-4}$M) | TPP($\times10^{-5}$M) | log $K_{EX}$ |
|---|---|---|
| 2.2 | 1.0 | 0.639 |
| 3.7 | 1.0 | 0.662 |
| 6.3 | 1.0 | 0.601 |

where $K_{EX}$ has been obtained from plots of log(TPP) concentration versus CAS distribution ratio.

Table 2.Transport of CAS across an artificial membrane using p-ethoxybenzyltriphenylphosphonium bromide (EBTP) as pairing ion.

| CAS($\times10^{-4}$M) | EBTP($\times10^{-4}$M) | %loss (60min) | CA($\times10^{-4}$M) | EBTP($\times10^{-4}$M) | %loss (60min) |
|---|---|---|---|---|---|
| 4.5 | 0 | 1.3 | 4.5 | 0 | 7.8 |
| 4.5 | 4.6 | 3.3 | 4.5 | 45.6 | 8.4 |
| 4.5 | 23.2 | 8.6 | | | |
| 4.5 | 46.0 | 12.3 | | | |

These data correlate well with findings from the perfusion studies with,for example, a clearance parameter value for CAS of $2.24\times10^{-4}$ mls.$min^{-1}$ (SD $9.5\times10^{-5}$,n=4) being raised to $3.23\times10^{-4}$ (SD $1.9\times10^{-4}$. n=4) in the presence of p-chloroBTP using ion-pair forming amounts. These results indicate that ion-pairing can be used to increase the ocular uptake of large organic ions, and that this effect is well simulated by the in vitro experiments

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0022-3573/81/120104P-01$02.50/0